## REMARKS

Restriction Requirement

Claims 16-19 and 31-37, directed to non-elected inventions, have been canceled without disclaimer of or prejudice to the subject matter therein. Applicants expressly reserve the right to pursue the subject matter of the non-elected claims in a divisional application without the need to file a terminal disclaimer.

Formal Drawings

The draftsperson has objected to the drawings filed on August 9, 2001. Corrected drawings have been submitted to the Drawing Review Board under separate cover.

Amendments:

Claim 1 has been amended to incorporate limitations from original Claims 2, 11, 15 and the specification, page 34, lines 3-9. Claim 3 has been amended to correct the dependency. Claim 15 has been amended to correct the antecedent basis. Claim 27 has been amended to correct the capitalization of the word "Nedocromil" and to correct the spellng of the word. The specification has also been amended to correct this word and also to correct the spelling of the word.

Objections to Claim 27 and the Disclosure:

The Examiner has objected to Claim 27 and the disclosure for presenting the term "Nedocromil" without capitalization. The disclosure and Claim 27 have been amended to correct this typographical error, including the misspelling of the word.

Objection to the Specification and Rejection of Claims 1-15 and 20-30 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1-15 and 20-30 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner contends that the specification is enabling only for a method to inhibit airway hyperresponsiveness (AHR) in a mammal by administering CGRP, but is not enabling for a method using any agent, any fragment

of CGRP, any homologue of CGRP or any product of rationale drug design; or said method incorporating any of the limitations of the dependent claims 2-15 or 20-30. The Examiner contends that it would require undue experimentation to select and use any of the agents encompassed by the claims to inhibit AHR.

Applicants traverse the rejection of Claims 1-15 and 20-30 under 35 U.S.C. § 112, first paragraph. Applicants initially note that the claims have been limited to recite CGRP peptides, fragments thereof that bind to and activate the CGRP receptor, homologues thereof that bind to and activate the CGRP receptor, and analogs thereof that bind to and activate the CGRP receptor. Applicants submit that the specification, combined with the knowledge regarding the structure and biological activity of CGRP in the art at the time of the invention, fully enable one of skill in the art to practice the claimed invention without undue experimentation.

First, Applicants respectfully note that the CGRP peptide is a small peptide of only 37 amino acids, and that both the α and β-isoforms of CGRP have been isolated and fully characterized by structure and basic function prior to the invention. The specification provides multiple references to the teachings of the nucleic acid and amino acid sequences of CGRP, including synthetic peptides of CGRP (page 26, line 24 to page 27, line 26). Moreover, production of fragments of a 37 amino acid peptide is well within the ability of those of skill in the art, and the specification, given the general skill in the art, teaches how one can test for the biological activity of the peptide or fragment (page 28, line 12 to page 29, line 21; and page 34, line 20 to page 35, line 5). Similarly, the specification teaches how to produce homologues of CGRP (page 28, lines 12-28; page 30, line 17 to page 31, line 2; page 34, lines 9-19;) and again, the ability to produce and test for the biological activity of such homologues is well within the ability of those of skill in the art, is taught by the specification (e.g., page 34, line 20 to page 35, line 5), and would not require undue experimentation. Contrary to the Examiner's contention, given the knowledge in the art of the structure of the small peptide (see page 26, line 24 to page 27, line 26), one of skill in the art would be readily able to select which amino acids can be modified in a homologue or fragment and retain CGRP activity. Indeed, the specification teaches that a fragment spanning amino acids 8-37 is an antagonist, providing guidance as to where modifications can not be tolerated to preserve the agonist function of CGRP. Moreover, the specification teaches that the peptide is highly homologous among animal

species and demonstrates that the peptide can be used interchangeably among species (see Examples, where human CGRP was used in mice). Therefore, one of skill in the art already has substantial information about the structure of CGRP and its correlation with function by comparing the sequences of CGRP among species. Such knowledge would allow the skilled artisan to predictably modify the peptide while maintaining the biological activity.

Furthermore, at the time of the invention, the art had already taught how to produce homologues and analogs of CGRP with biological activity. For example, U.S. Patent No. 4,720,483, a copy of which is enclosed, teaches acylated and amidated forms of CGRP as well as simple methods for synthesizing and modifying the peptide. Similarly, PCT Publication No. WO 89/03686 (copy enclosed) teaches CGRP analogs with biological activity. Other analogs are described in the specification (e.g., page 34, line 26 to page 35, line 5; page 35, line 20 to page 37, line 3). Therefore, methods for the production of CGRP fragments, homologues and analogs with biological activity are already known in the art and could be predictably and readily extended to the production of new fragments, homologues and analogs.

With regard to the use of such fragments, homologues and analogs in the claimed method, Applicants have demonstrated that CGRP effectively inhibits and prevents airway hyperresponsiveness in an art-accepted murine model of allergic airway hyperresponsiveness. This model has been demonstrated prior to the present invention to be an accepted model of airway hyperresponsiveness induced by allergic inflammation, which shares many characteristics with human respiratory conditions associated with allergic inflammation. This murine model has been published extensively (For example, Renz et al., 1992, *J. Allergy Clin. Immunol.* 89:1127-1138; Larsen et al., 1992, *J. Clin. Invest.* 89:747-752; and Saloga et al., 1993, *J. Clin. Invest.* 91:133-141). Therefore, the model has been established as useful for evaluating compounds that can be used to treat allergen-induced AHR and positive results with this model using CGRP are predictive that fragments, homologues and analogs of CGRP that have the biological activity of CGRP will also be useful. The Examiner points to a publication of Zhu et al. to support a position that use of other CGRP homologues will be unpredictable. However, Applicants submit that the use of the art-accepted model of allergen-induced AHR in the present specification to demonstrate a role for the

administration of CGRP is sufficient to demonstrate to one of skill in the art the predictability of the claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-15 and 20-30 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claims 1-15 and 20-30 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1-15 and 20-30 under 35 U.S.C. § 112, first paragraph, on the basis of written description. Specifically, the Examiner contends that the specification does not reasonably provide a written description of the structure associated with the function of any agent, any fragment of CGRP, any homologue of CGRP, any product of rationale drug design or any CGRP RAMP.

Applicants traverse the Examiner's rejection of Claims 1-15 and 20-30 under 35 U.S.C. § 112, first paragraph. As discussed above, Applicants submit that the CGRP peptide is a small peptide of only 37 amino acids, and that both the α and β-isoforms of CGRP have been isolated and fully characterized by sequence and structure prior to the invention. The specification provides multiple references that teach the nucleic acid and amino acid sequences of CGRP, including synthetic peptides of CGRP. The specification also provides guidance regarding how to produce fragments, homologues and analogs of CGRP (page 28, line 12, to page 37, line 3) and how to identify whether such fragments, homologues and analogs have CGRP activity (page 28, line 12 to page 29, line 21; and page 34, line 20 to page 35, line 5). The structure of the CGRP peptide has been *well characterized* and is known for several animal species, and the specification demonstrates that the peptide can be used interchangeably among species due to high homology between species (see Examples, where human CGRP was used in mice). This disclosure shows that the structure is highly conserved and provides evidence that one of skill in the art would be able to envision what structures of homologues and analogs of CGRP would be predicted to have biological activity. Additionally, as discussed above, at the time of the invention, CGRP analogs were known in the art. Therefore, one of skill in the art would be able to readily envision the genus of fragments, homologues and analogs of CGRP that meet the requirements of having CGRP biological activity

due to the extensive knowledge regarding the structure and general function of the peptide in the art and indeed, due to the availability in the art of multiple compounds meeting the claim limitations at the time of the invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-15 and 20-30 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-5, 8-9, 11, 20, 23, 26 and 29 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1-5, 8-9, 11, 20, 23, 26 and 29 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Nagase et al. Specifically, the Examiner asserts that Nagase et al. teach a method of inhibiting AHR in a mammal by administering an agent, such as CGRP, in the lungs exposed to allergen such as methacholine induced airway hyperresponsiveness. The Examiner further contends that various embodiments of dependent claims are also taught by Nagase et al.

Applicants traverse the rejection of Claims 1-5, 8-9, 11, 20, 23, 26 and 29 under 35 U.S.C. § 102(b). Initially, it is noted that Claim 1 has been amended to more particularly describe that the present method is directed to the treatment of allergen-induced AHR. Nagase et al. do not teach or suggest a method of treating allergen-induced AHR. Rather, Nagase et al. teach the administration of CGRP to animals in which airway constriction is induced by hyperpnea challenge via exposure to dry gas. The model studied by Nagase et al. mimics a type of airway hyperresponsiveness that results from deep and rapid breathing, particularly of cold, dry air such as occurs in exercise-induced asthma (Nagase et al., page 1551, first paragraph). Hyperpnea-induced AHR has a different cause and different general pathophysiology than allergen-induced AHR. As discussed in Nagase et al., hyperpnea challenge causes constriction a few moments after challenge, resolves spontaneously, is reproducible upon identical challenge, and is believed to be associated with tachykinins and sensory nerves (e.g., see page 1554-1555). In contrast, allergen-induced AHR is induced by sensitization to and subsequent challenge with an allergen, and is associated with an immune (IgE) response, a dependence on a Th2-type response, and an eosinophil response, and is both a marked and evolving hyperresponsiveness of the airways (see page 12, lines 1-8 of the specification). One of skill in the art will understand that a method to treat hyperpnea-induced AHR is not equivalent to a method to

treat allergen-induced AHR, nor can the usefulness of a compound in hyperpnea-induced AHR be simply extrapolated be useful in allergen-induced AHR, since these are different conditions.

In the July 29 Office Action, the Examiner frequently refers to experiments in Nagase et al. which use methacholine- and endothelin-1-induced constriction in support of the rejection, and additionally references exposure to allergen. First, Applicants note that the use of methacholine as an inducer of constriction in Nagase et al. should not be confused with the experimental model of the present invention, which is a model of allergen-induced airway hyperresponsiveness in which methacholine is used as a provoking stimulus, but only *after* the subject is sensitized to and challenged with an allergen. It is noted that in general, methacholine is only used as a pharmacological agent to assist in the measurement of AHR in a variety of experimental protocols, but is not to be confused with an allergen. Nagase et al. administer methacholine alone as an inducer of constriction *in the absence of* any allergen sensitization and challenge, and therefore is not using a model of allergen-induced airway hyperresponsiveness. In any event, Applicants respectfully note that in the methacholine and endothelin-1 experiments, Nagase et al. in fact saw no effect on airway constriction from the administration of CGRP (see Fig. 5 of Nagase et al.). Figs. 2 and 3 as referenced by the Examiner related to hyperpnea-induced AHR.

In view of the foregoing remarks, it is submitted that Nagase et al. do not teach or suggest a method of treating allergen-induced airway hyperresponsiveness using an agent that binds to and activates a CGRP receptor as presently claimed, and Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-5, 8-9, 11, 20, 23, 26 and 29 under 35 U.S.C. § 102(b).

Rejection of Claims 1-11, 21-24, 27, 29 and 30 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1-11, 21-24, 27, 29 and 30 under 35 U.S.C. § 102(b), contending that these claims are anticipated by U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478. Specifically, the Examiner contends that these patents teach a method of using CGRP and homologues thereof to inhibit acute or chronic inflammatory conditions such as asthma, which the Examiner asserts is associated with AHR. The Examiner further contends that various embodiments of dependent claims are also taught by the '978 or '478 patents.

Applicants traverse the rejection of Claims 1-11, 21-24, 27, 29 and 30 under 35 U.S.C. § 102(b). It is submitted that neither the '978 patent nor the '478 patent teaches or suggests a method to treat allergen-induced airway hyperresponsiveness by administration of an agent that binds to and activates a CGRP receptor as presently claimed. The '978 patent and the '478 patent are directed to the use of CGRP to ameliorate inflammatory conditions by inhibiting the release of the proinflammatory cytokines, IL-1, or IL-1 and IL-2, from immune cells such as macrophages and lymphocytes. The use of CGRP is disclosed by these patents as being useful for the treatment of a wide variety of diseases, including pain, orthopedic dysfunction, viral diseases, acute and chronic inflammatory conditions, wound healing, edema, arthritis, diseases of the urinary tract and of joints, autoimmune diseases, anaphylactic conditions, shock, tendonitis, osteoarthritis, nonsurgical disc syndrome, myositis, graft rejection, and allergic reactions, with asthma being mentioned among the allergic reactions (column 13, line 6) or as an acute shock condition (column 7, line 34). CGRP is also stated to be useful in an oral contraceptive. However, neither patent teaches or suggests using CGRP to treat *airway hyperresponsiveness*.

First, it is submitted that the Examiner appears to have equated asthma with airway hyperresponsiveness (AHR), which is not correct. Asthma is a lung disease that is typically characterized by periodic airflow limitation and/or hyperresponsiveness to a *variety* of stimuli which results in excessive airways narrowing. There are different types of asthma which reflect the etiology and more specific pathology of the disease (e.g., exercise-induced asthma, allergic asthma, pollution-induced asthma, occupational asthma). AHR is a condition that is associated with asthma, but AHR can also have different causes and pathophysiologies. Moreover, even allergen-induced AHR can be associated with diseases other than asthma (e.g., allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, allergic bronchitis bronchiectasis, hypersensitivity pneumonitis, reactive airway disease syndrome, hyper-eosinophilic syndrome, rhinitis, sinusitis, and parasitic lung disease). In the most general terms, AHR is characterized as an abnormality of the airways that allows them to narrow too easily and/or too much in response to a stimulus capable of inducing airflow limitation. AHR can be a functional alteration of the respiratory system caused by inflammation in the airways or from airway remodeling (*e.g.*, such as by collagen deposition), and can be caused, for example, by collagen deposition, bronchospasm, airway smooth muscle hypertrophy, airway smooth muscle

contraction, mucous secretion, cellular deposits, epithelial destruction, alteration to epithelial permeability, alterations to smooth muscle function or sensitivity, abnormalities of the lung parenchyma and cellular infiltrates in and around the airways. Therefore, asthma and AHR are not one in the same condition, but rather conditions that can be associated with one another.

At most, the '978 and '478 patent teach the inhibition of inflammation associated with the production of proinflammatory cytokines for treatment of an extremely wide variety of diseases and conditions, among which asthma is listed. On this point, Applicants emphasize the distinction between asthma and AHR by submitting that one could treat inflammation associated with asthma *without* treating AHR. It is agreed that the '978 and '478 patents teach inhibition of inflammation, but it is submitted that neither of the '978 patent nor the '478 patent teaches using CGRP or a related agent to reduce or inhibit airway constriction and in particular, to treat AHR.

Second, even if the Examiner construes the patents as teaching conditions that generally or inherently might encompass the treatment of AHR, Applicants submit that not only do the cited patents fail to *specifically* teach the treatment of allergen-induced AHR, the patents teach the use of CGRP to treat inflammation in such an incredibly broad variety of diseases and conditions that the reference as a whole *fails* to teach or suggest the claimed method for treatment of allergen-induced AHR with *sufficient specificity* to anticipate the claimed invention. The cited patents describe the use of CGRP and related peptides to treat diseases and conditions of vastly different pathophysiologies, from viral infections, to orthopedic dysfunction, to pain, to allergic reactions, to graft rejection, to autoimmune disease, and even for use as a contraceptive. The list of diseases and Applicants submit that the large listing of diseases and conditions is not sufficiently limited or well delineated enough to teach or suggest using CGRP to treat allergen-induced AHR.

This argument is bolstered by the explicit teaching by both the '978 patent and the '478 patent that CGRP is specifically used to inhibit the release of the proinflammatory cytokines, IL-1, or IL-1 and IL-2, from immune cells such as macrophages and lymphocytes. First, as discussed above, treatment of inflammation does not lead one of skill in the art to contemplate the treatment of AHR, because treatment of inflammation can occur in the absence of an effect on AHR, as these are separate conditions. Second, even with an association between inflammation and allergen-induced AHR, Applicants submit that the suggestion to inhibit the release of IL-1 or IL-1 and IL-2 in a patient

with allergen-induced AHR or indeed, any allergic inflammation, including allergic asthma, is not consistent with, and in fact is *contrary to*, what is known about allergic inflammation by those of skill in the art. As set forth in the specification (page 5, lines 17-27), it was known in the art at the time of the invention that the allergic inflammation is mediated by a T helper type 2 (Th2) response, which involves the release of cytokines such as IL-4, IL-5 and IL-13, and which can generally be downregulated by the opposing cytokines of a T helper type 1 (Th1) immune response, such as IFNγ and IL-12. IL-12, IL-1 and IL-6 are produced by macrophages and IFNγ, a stimulator of macrophage activity, is produced by Th1-type lymphocytes (in addition to IL-2). Therefore, the inhibition of these immune cells and cytokines would not be expected by those of skill in the art to be useful to treat allergic inflammation, and even if one of skill in the art viewed the large genus of conditions that are explicitly disclosed by the '978 and '478 patents, such teachings would not lead to the conclusion that allergen-induced AHR, which was not specified in these patents, could be treated by administration of CGRP.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-11, 21-24, 27, 29 and 30 under 35 U.S.C. § 102(b).

Rejection of Claims 1 and 25 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 25 under 35 U.S.C. § 103, contending that these claims are unpatentable over Nagase et al. or U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, each in view of Suissa et al. The Examiner refers to the prior discussion of the teachings of Nagase et al., the '978 patent and the '478 patent, and contends that Suissa et al. teach leukotriene receptor antagonists are more effective than beta-agonist alone in treating mild-to-moderate asthma, and a decrease in FEV1 of at least 55% of the predicted value. The Examiner asserts that it would have been *prima facie* obvious to combine the teachings above to arrive at a teaching of administration of CGRP with other agents.

Applicants traverse the rejection of Claims 1 and 25 under 35 U.S.C. § 103. Initially, Applicants refer to the discussion above with regard to the rejections under § 102 and submit that none of Nagase et al., U.S. Patent No. 5,858,978, or U.S. Patent No. 5,635,478, teach or suggest a method to inhibit allergen-induced airway hyperresponsiveness by administering to an animal an

agent with CGRP biological activity as presently claimed. Moreover, the combination of any or all of these references with Suissa et al. does not remedy the deficiencies of the primary references. Suissa et al. teach the use of leukotriene receptor antagonists and beta agonists to treat asthma, and do not teach or suggest using CGRP to treat allergen-induced airway hyperresponsiveness.

More specifically, in order to be *prima facie* obvious, a combination of references must: (1) teach each and every element of the claimed invention; (2) provide a motivation to make the combination and arrive at the claimed invention; and (3) provide a reasonable expectation of success at being able to practice the claimed invention.

The combination of any of the primary references with Suissa et al. fails to teach each and every element of the invention as discussed above.

With regard to motivation to combine the references and/or arrive at the present invention, Nagase et al. provides no motivation to treat allergen-induced AHR because results with hyperpnea-induced AHR can not be simply extrapolated to a type of AHR having a different etiology and pathophysiology. Even combined with Suissa et al., at best the combination might motivate one of skill in the art to use leukotriene antagonists with beta agonists to treat asthma or leukotriene antagonists to treat hyperpnea-induced AHR, but would not provide any motivation with regard to the claimed invention. With regard to the '978 or '478 patents, as discussed above, the suggestion to inhibit the release of IL-1 or IL-1 and IL-2 in patient with allergic inflammation, is not consistent with, and in fact is contrary to, what is known about allergic inflammation by those of skill in the art. As set forth in the specification, the present inventors have demonstrated experimentally that the inhibition of IL-1 *in vivo* does not have any effect on airway hyperresponsiveness, via anti-IL-1 administration, IL-1 receptor antagonists or IL-1 knockout mice. Therefore, one of skill in the art of allergic inflammation and particularly, allergic inflammation of the respiratory system, would not, based on the teachings of either patent, be motivated to look to the use of CGRP to treat allergic inflammation or airway hyperresponsiveness. Even in combination with Suissa et al., there is no motivation to arrive at the invention because Suissa et al. is only directed to the use of leukotriene receptor antagonists with beta-agonists to treat asthma.

With regard to expectation of success, the combination of Nagase et al. and Suissa et al. provide no expectation of success, because one of skill in the art would not have an expectation that

a result produced in hyperpnea-induced AHR shown by Nagase et al. would necessarily be operable in the different condition of allergen-induced AHR and Suissa et al. is directed to the use of an entirely different compound for the treatment of asthma and therefore can not contribute to any expectations with regard to CGRP. With regard to the '978 or '478 patents, one of skill in the art of allergic inflammation and particularly, allergic inflammation of the respiratory system, would not, based on the teachings of either patent, be motivated to look to the use of CGRP to treat allergic inflammation or airway hyperresponsiveness, and in fact would be *dissuaded* from doing so based on a complete lack of expectation of success for the reasons previously discussed here. Combination with Suissa et al. does not remedy the deficiencies in expectation of success, because the teachings of Suissa et al. are not related to the claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 25 under 35 U.S.C. § 103.

Rejection of Claims 1 and 27 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 27 under 35 U.S.C. § 103, contending that these claims are unpatentable over Nagase et al. or U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, each in view of Drazen et al. or Abraham et al. or Abdelaziz et al. or Barnes et al or Hoshino et al. The Examiner refers to the prior discussion of the teachings of Nagase et al., the '978 patent and the '478 patent, and contends that: (1) Drazen et al. teach that leukotriene receptor antagonists are safe and effective asthma treatment; (2) Abraham et al. teach agents such as cromolyn sodium and beta 2 mimetic reproterol hydrochloride in combination gives better protection against post-antigen-induced AHR; (3) Abdelaziz et al. teach agents such as Nedocromil can reduce AHR; (4) Barnes et al. teach agents such as theophylline for treatment of asthma; (5) Hoshino et al. teach an agent such as ketotifen is beneficial for inhibiting activated eosinophils and T cell infiltration into the airways. The Examiner asserts that it would have been obvious to combine the teachings above to arrive at a teaching of administration of CGRP with other agents.

Applicants traverse the rejection of Claims 1 and 27 under 35 U.S.C. § 103. Applicants again refer to the discussion of Nagase et al. and of U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478 presviously herein, and submit that, for the reasons above, none of these references

teaches or suggests a method to inhibit allergen-induced airway hyperresponsiveness by administering to an animal an agent with CGRP biological activity as presently claimed. The combination of any or all of these references with any or all of Drazen et al., Abraham et al., Abdelaziz et al., Barnes et al. or Hoshino et al. does not remedy the deficiencies of the primary references, because each of these references is directed to completely different agents that could be used to treat asthma or AHR, but none teach or suggest the claimed method or the use of CGRP.

The combination of references also fails to provide any motivation to make the combination as the Examiner has done or any expectation of success at making and using the claimed invention. The deficiencies of the primary references in these regards have been discussed in detail above. None of the secondary references cited in this rejection provides motivation to do anything but use a completely different agent for a condition specified in that reference. Similarly, none of these references is directed to the use of CGRP for any reason and so none of these references can remedy the lack of expectation of success in the primary references.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 27 under 35 U.S.C. § 103.

Rejection of Claims 1 and 12-14 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 12-14 under 35 U.S.C. § 103, contending that these claims are unpatentable over Nagase et al. or U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, each in view of Cadieux et al. The Examiner refers to the prior discussion of the teachings of Nagase et al., the '978 patent and the '478 patent, and contends that Cadieux et al. teach administering an agent such as CGRP in various doses which allegedly caused a dose related inhibition of substance P induced bronchconstriction in guinea pigs presensitized to allergen. The Examiner asserts that it would have been *prima facie* obvious to combine the teachings above to arrive at a teaching of administration of CGRP at a dose taught by Cadieux et al.

Applicants traverse the rejection of Claims 1 and 12-14 under 35 U.S.C. § 103. Applicants again refer to the discussion of Nagase et al. and of U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, and submit that, for the reasons above, none of these references teaches or suggests a method to inhibit allergen-induced airway hyperresponsiveness by administering to an animal an

agent with CGRP biological activity as presently claimed. The combination of any or all of these references with Cadieux et al. does not remedy the deficiencies of the primary references, because Cadieux et al. teach that CGRP inhibits bronchoconstriction that is not induced by allergen (similar to Nagase et al.), and further teach that CGRP was found to be *ineffective* against the constriction in inflammatory conditions. Therefore, not only does the combination of any of the primary references with Cadieux et al. fail to teach or suggest the claimed method, the combination does not motivate one of skill in the art to arrive at the invention and provides no expectation of success because Cadieux et al. actually *dissuade* one of skill in the art from arriving at the claimed method by concluding that the use of CGRP in inflammatory conditions is inoperable. This is effectively a *teaching away* from the claimed invention. The teaching of doses by Cadieux et al. does not remedy any deficiencies of the combination of references.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 12-14 under 35 U.S.C. § 103.

Rejection of Claims 1 and 15 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 25 under 35 U.S.C. § 103, contending that these claims are unpatentable over Nagase et al. or U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, each in view of PCT Publication No. WO 97/09046. The Examiner refers to the prior discussion of the teachings of Nagase et al., the '978 patent and the '478 patent, and contends that WO 97/09046 teaches various agents, such as ligand, which is CGRP RAMP, to inhibit asthma. The Examiner asserts that it would have been *prima facie* obvious to combine the teachings above to substitute CGRP for a method to inhibit AHR comprising administering a product of rationale drug design that binds to and activates a CGRP receptor.

Applicants traverse the rejection of Claims 1 and 15 under 35 U.S.C. § 103. Applicants again refer to the discussion of Nagase et al. and of U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, and submit that, for the reasons above, none of these references teaches or suggests a method to inhibit allergen-induced airway hyperresponsiveness by administering to an animal an agent with CGRP biological activity as presently claimed. The combination of any or all of these references with PCT Publication No. WO 97/09046 does not remedy the deficiencies of the primary

references, because this reference does not teach or suggest the claimed method or the use of CGRP. WO 97/09046 teaches the use of quinine or quinidine antagonists of CGRP receptor to treat CGRP-mediated disorders.

Furthermore, Applicants do not find a disclosure of CGRP receptor activity modifying protein (RAMP) in WO 97/09046 and certainly, CGRP RAMP is not an antagonist of CGRP receptor. Rather, RAMP *enhances* the biological activity of CGRP (see specification, page 44, lines 7-18). Therefore, CGRP RAMP would not be encompassed even implicitly by the teachings of WO 97/09046. Moreover, WO 97/09046 teach that one should inhibit the CGRP receptor to treat conditions, not activate the receptor, which is a direct teaching away from the method of the present invention. Therefore, WO 97/09046, alone or in combination with the primary references, not only fails to make up for the deficiencies of the primary references, but also provides a direct *teaching away* from the present invention, since the reference teaches the use of antagonists of the CGRP receptor. Therefore, there is no motivation or expectation of success of making and using the invention in view of the combination.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 15 under 35 U.S.C. § 103.

Rejection of Claims 1 and 28 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 28 under 35 U.S.C. § 103, contending that these claims are unpatentable over Nagase et al. in view of PCT Publication No. WO 97/09046. The Examiner refers to the prior discussion of the teachings of Nagase et al. and contends that WO 97/09046 teach that CGRP RAMP binds to and activates a CGRP receptor to inhibit asthma. The Examiner asserts that it would have been *prima facie* obvious to combine the teachings above to arrive at a teaching of administration of CGRP with CGRP RAMP.

Applicants traverse the rejection of Claims 1 and 28 under 35 U.S.C. § 103. Applicants again refer to the discussion above with regard to the combination of Nagase et al. with PCT Publication No. WO 97/09046 and submit that none of these references, alone or in combination, teaches or suggests a method to inhibit allergen-induced airway hyperresponsiveness by administering to an animal an agent with CGRP biological activity as presently claimed. Further, the combination of

WO 97/09046 with Nagase et al. not only fails to make up for the deficiencies of the primary reference, but also provides a direct *teaching away* from the present invention, since the claims are directed to activating the CGRP receptor, not antagonizing the receptor. Therefore, there is no motivation or expectation of success of making and using the invention in view of the combination.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 28 under 35 U.S.C. § 103.

Rejection of Claims 1 and 28 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 28 under 35 U.S.C. § 103, contending that these claims are unpatentable over U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478, each in view of PCT Publication No. WO 97/09046. The Examiner refers to the prior discussion of the teachings of the '978 patent and the '478 patent, and contends that WO 97/09046 teaches that CGRP RAMP binds to and activates a CGRP receptor to inhibit asthma. The Examiner asserts that it would have been *prima facie* obvious to combine the teachings above to substitute the corticosteroid or the phosphodiesterase as taught by the U.S. patents for the CGRP RAMP to inhibit AHR.

Applicants traverse the rejection of Claims 1 and 28 under 35 U.S.C. § 103. Applicants again refer to the discussion above with regard to the combination of either the '978 patent or the '478 patent with PCT Publication No. WO 97/09046 and submit that none of these references, alone or in combination, teaches or suggests a method to inhibit allergen-induced airway hyperresponsiveness by administering to an animal an agent with CGRP biological activity as presently claimed. Further, the combination of WO 97/09046 with either patent not only fails to make up for the deficiencies of the primary references, but also provides a direct *teaching away* from the present invention, since the claims are directed to activating the CGRP receptor, not antagonizing the receptor. Therefore, there is no motivation or expectation of success of making and using the invention in view of the combination.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 28 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the Examiner's concerns as set forth in the July 29 Office Action. In the event that the Examiner has any questions or concerns regarding Applicants' position, please contact the below-named agent at (303)863-9700.

Respectfully submitted,

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Date: January 29, 2003

In the Specification:

The paragraph spanning lines 11-17 of page 8 has been amended as follows:

--In one embodiment, the agent is administered to the mammal in conjunction with another agent selected from the group consisting of: corticosteroids, (oral, inhaled and injected), β-agonists (long or short acting), leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, phosphodiesterase inhibitors, sodium cromoglycate, [nedocrimal]Nedocromil, and theophylline. In another embodiment, the agent is administered to the mammal in conjunction with a CGRP receptor activity modifying protein (RAMP). In another embodiment, the agent is administered in a pharmaceutically acceptable excipient.--

The paragraph spanning lines 19-25 of page 44 has been amended as follows:

--In another embodiment, the agent that binds to and activates a CGRP receptor according to the present invention can be administered in conjunction with another compound or agent that is useful for treating allergen-induced airway hyperresponsiveness in the patient. Such an agent, includes, but is not limited to: corticosteroids, (oral, inhaled and injected), β-agonists (long or short acting), leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, phosphodiesterase inhibitors, sodium cromoglycate, [nedocrimal]Nedocromil, and theophylline.--

In the Claims:

Claims 2, 11, 16-19 and 31-37 have been canceled.

Claims 1, 3, 15 and 27 have been amended as shown below.

Claims 4-10, 12-14, 20-26 and 28-30 have not been changed.

Claims 38-41 have been added.

1. (Once Amended) A method to inhibit allergen-induced airway hyperresponsiveness in a mammal, comprising administering to a mammal an agent selected from the group consisting of calcitonin gene related peptide (CGRP), a fragment of CGRP that binds to and activates a CGRP receptor, a homologue of CGRP that binds to and activates a CGRP receptor, and a CGRP analog that binds to and activates a CGRP receptor, wherein said agent [that] binds to and activates a calcitonin gene related peptide (CGRP) receptor in the lungs of said mammal, wherein said mammal

has, or is at risk of developing, airway hyperresponsiveness, wherein administration of said agent inhibits allergen-induced airway hyperresponsiveness in said mammal.

3. (Once Amended) The method of Claim [2]1, wherein said mammal has been sensitized to an allergen and has been exposed to, or is at risk of being exposed to, an amount of said allergen that is sufficient to induce airway hyperresponsiveness (AHR) in said mammal in the absence of said agent.

15. (Once Amended) The method of Claim 1, wherein said [agent] analog is a product of rational drug design that binds to and activates a CGRP receptor.

27. (Once Amended) The method of Claim 1, wherein said agent is administered to said mammal in conjunction with another agent selected from the group consisting of: corticosteroids, (oral, inhaled and injected), β-agonists (long or short acting), leukotriene modifiers (inhibitors or receptor antagonists), antihistamines, phosphodiesterase inhibitors, sodium cromoglycate, [nedocrimal]Nedocromil, and theophylline.